USP DQI trip to follow up on the program activities in Ethiopia

Addis Ababa - Ethiopia
May 11-15, 2009

Trip Report

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Cooperative Agreement # HRN-A-00-00-00017-00
Sponsoring USAID Missions: USAID Mission – Ethiopia, PMI Program
Grantee: United States Pharmacopeia Drug Quality and Information (USP DQI) Program
Author(s) Name: USP DQI Staff
Language: English
Date of Publication: June 12, 2009

This report is made possible by the generous support of the American people through the United States Agency for International Development (USAID), under Cooperative Agreement number HRN-A-00-00-00017-00. The contents are the responsibility of the U. S. Pharmacopeia Drug Quality and Information Program and do not necessarily reflect the views of the United States Government.

About USP DQI

The United States Pharmacopeia Drug Quality and Information (USP DQI) Program, funded by the U.S. Agency for International Development (USAID), provides technical leadership to more than 30 developing countries to strengthen their drug quality assurance programs, ensure the quality of medicines and promote public health. USP DQI helps build local, national and regional capacity to improve the standards of drug manufacturing and distribution, reduce the impact of infectious diseases, mitigate the effects of the HIV/AIDS epidemic, and advance the appropriate use of medicines. This document does not necessarily represent the views or opinions of USAID. It may be reproduced if credit is given to USP DQI.

Abstract

USP DQI, together with local stakeholders, established a Medicines Quality Monitoring (MQM) program in five sentinel sites in Oromia region. Coordinated by the quality control (QC) lab of the Ethiopian Drug Regulatory Authority (DACA) and its regional bureaus, the first phase of MQM consisted of sampling and testing selected antimalarials and controlling their quality using basic tests with Minilabs®. The first phase was not completed according to the program guidelines, and the purpose of this mission is to review all program activities and take the necessary actions to complete the second phase as per the program deadlines.

The DQI team will also follow up on other ongoing activities with DACA and DACA QC lab.

Recommended Citation

Smine, A. and Wondemagegnehu, E. 2009. USP DQI trip to follow up on the program activities in Ethiopia; Addis Ababa, Ethiopia, May 11-15, 2009. Submitted to the U.S. Agency for International Development by the United States Pharmacopeia Drug Quality and Information Program. Rockville, Maryland: United States Pharmacopeia.

Key Words

Quality Control, Antimalarial Drugs, Sentinel Sites, Minilab, Drug quality monitoring program, USP DQI, Food and Drug Board of Ghana, MCP

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ACKNOWLEDGEMENTS

The USP DQI team would like to express sincere appreciation to DACA staff for their time and hard work. Special thanks go to Mr. Yehulu Denekew, Director General; Mr. Mengisteab Woldearegay, Deputy Director; Mr. Wonde Alemu, Director, Standards; Mr. Bikila Bayissa, Director Drug Quality Control and Toxicology Laboratory (DQCTL); and all QC lab staff.

The authors wish to express their appreciation to the USP DQI administrative staff and editors for their assistance with logistical arrangements and for editing the trip report.

Finally, the authors would like to thank the USAID/Ethiopia Mission, in particular, Mr. Richard Reithenger, PMI Team Leader; the Malaria Operational Plan (MOP) team members from USAID and Centers for Disease Control and Prevention (CDC), and Mr. Anthony Boni and Ms. Veerle Coignez at USAID/Washington for their guidance and helpful insights.

ACRONYMS

ACT	Artemisinin-based Combination Therapy
CTO	Cognizant Technical Officer
DACA	Drug Administration and Control Authority
DQ	Drug Quality
DQCTL	Drug Quality Control and Toxicology Laboratory
DRA	Drug Regulatory Authority
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
HPLC	High Performance Liquid Chromatography
MOH	Ministry of Health
MOP	Malaria Operational Plan
MSH/RPM+/SPS	Management Sciences for Health/Rational Pharmaceutical Management Plus/Strengthening Pharmaceutical Systems
PMI	President's Malaria Initiative
PMS	Post Marketing Surveillance
QA	Quality Assurance
QC	Quality Control
RS	Reference Standard
SP	Sulfadoxine-Pyrimethamine
SOP	Standard Operating Procedure
USAID	United States Agency for International Development
USP DQI	United States Pharmacopeia Drug Quality and Information
USP-NF	United States Pharmacopeia-National Formulary
WHO	World Health Organization

Background

USP DQI was selected by USAID/Ethiopia to provide technical, strategic, and operational support to strengthen the quality control of antimalarial medicines in Oromia. The USAID/Ethiopia Office of Health, AIDS, Population and Nutrition believes that post marketing surveillance will contribute to the Mission's efforts in malaria diagnosis, treatment, prevention, and control under the President's Malaria Initiative (PMI).

USP DQI conducted a two-day Micro-Planning Workshop in July 2008 on establishing a post marketing surveillance (PMS) program to monitor the quality of antimalarial medicines in Oromia Region. In August 2008, USP DQI organized a training of the Drug Administration and Control Authority (DACA) Drug Quality Control and Toxicology Laboratory (DQCTL) staff as well as representatives from regional health bureaus. The PMS program was established in five sentinel sites, and the first round of antimalarial collecting has been completed at the sentinel sites level. DACA DQCTL is conducting confirmatory testing following USP DQI protocol.

To build DACA DQCTL's capacity, USP DQI received funds from the President's Emergency Plan for AIDS Relief (PEPFAR) under a sub-contract between USP DQI and Management Sciences for Health, Strengthening Pharmaceutical Systems (MSH-SPS). Under this sub-contract, USP DQI trained nine DQCTL analysts on good laboratory practices, HPLC, and dissolution. Soon after, DQI submitted a plan that DQCTL needs to implement with USP DQI support to reach a level of competency to qualify the lab for ISO 17025 accreditation.

USP DQI evaluated the data from the first phase of the drug quality monitoring program and concluded that a re-training was necessary in order to improve the quality of data generated. Additionally, the visit was used to discuss the revised protocol for drug quality monitoring with succinct steps about how to collect, analyze and properly report the data

Purpose of Trip

USP DQI staff traveled to Addis Ababa, Ethiopia to:

1. Meet with the Malaria Operation Plan (MOP) team
2. Review all first phase data, identify the root cause of the issues, and find solutions to continue the drug quality control of samples already collected as per the work plan
3. Meet with DACA Director and Deputy Director to discuss issues about the PMS program
4. Review, amend, and approve the DQCTL implementation plan

Source of Funding

This trip was supported by funds from USAID/Ethiopia.

Overview of Activities

Meeting with USAID and MOP team

Participants: Richard Greene, Michael MacDonald, and Peter Mamacos (USAID/Washington); Scott Filler and Manoj Menon (CDC/Atlanta), Richard Reithenger (USAID/Ethiopia-PMI), Abdelkrim Smine and Eshetu Wondemagegnehu (USP DQI)

After a brief introduction of all participants, Mr. Reithenger presented the USP DQI program and USAID support to Ethiopia on drug quality within PMI. The MOP team then focused on the progress of USP DQI/PMI activities, the work plan for 2010, and proposed activities for 2011.

Dr. Smine said that overall, activities are still going according to plan, even though DACA staff have been going through many staff changes, along with meetings and trainings. For the current work plan, DACA staff are repeating TLC on all collected samples and performing confirmatory tests at DACA labs. Dr. Smine feels that sampling was done incorrectly and that the sentinel site staff did not comply with procedures and guidelines provided by USP DQI. Data was not properly documented and reported. However, Dr. Smine is confident that USP DQI will face similar issues in other countries, and the first round of a new monitoring program is often a "learning experience." USP DQI will take the necessary actions so that future rounds of sampling and testing will be done according to the program procedures.

Dr. Wondemagegnehu and Dr. Smine shared USP DQI's proposed work plan and explained to the MOP team that with the funds allotted for next year, USP DQI sees that the priority is to continue the PMS program and expand it to two additional sentinel sites outside Oromia region. The two new sites will be selected by USP DQI, together with local stakeholders, based on solid selection criteria. Two rounds of sampling and testing will be done from the seven sentinel sites.

Mr. Greene asked about what USP DQI plans for FY10. Dr. Smine gave the participants a draft proposed work plan in which USP DQI proposes to expand its activities to other areas to address the gaps in the quality assurance systems in Ethiopia. The main activities include strengthening drug registration, assisting local medicines manufacturers by arranging GMP training programs, and supporting the new DQCTL lab to gain international accreditation.

The MOP team asked several questions related to how drug quality data could be used to advocate for enforcement actions and discussed how drug registration could improve drug quality assurance in Ethiopia. Dr. Smine and Dr. Wondemagegnehu gave examples and lessons learned from similar programs in other parts of the world. The discussion was fruitful and shed light on the gaps in the quality assurance of medicines in Ethiopia. The meeting was a good opportunity for the DQI team to explain the outcomes of drug quality control using basic tests and how such programs are vital in a large country with limited capacities and resources like Ethiopia.

Meeting with DACA

Participants: Mr. Yehulu Denekew, Director General, Mr. Mengisteab Woldearegay, Deputy Director General, and Mr. Wonde Alemu, Director of Standards (DACA); Mr. Bikila Bayissa, Director (DQCTL); and USP DQI Team

The USP DQI team briefed the group about the objectives of the visit and the meeting between the USP DQI and MOP teams. Dr. Smine then proposed discussing four issues: ongoing sentinel sites activities, FY 09 plans, the implementation plan for QC lab, and the new DACA QC lab.

The DQI team informed the Director and his team about the delay in conducting the sentinel sites activity as planned. The Director of Standards (former QC Lab Director) stated that the delay

was mainly caused by the fact that the DACA staff has been going through many changes and training during the Business Process Re-engineering (BPR) process that DACA has implemented. Dr. Smine added that in addition to this, there were other issues related to the quality of work delivered. For example, the sentinel site staff did not follow the guidelines and procedures provided to them during the training. Though part of the program, no supervisory visits to sentinel sites were taken. The Director and his deputy were very supportive and asked that the director of the lab and the DQI team find the root cause of the problems and make sure that the next round is carried with utmost professionalism. Dr. Smine reassured the participants that sample analysis and the report will be done according to the work plan. The USP DQI team was assured that the communication between USP DQI and DQCTL will improve so that follow-up on program activities will be more efficient.

The USP DQI team presented the draft work plan for the coming year, explaining to the participants that USP DQI has received the same level of funding and that the major activities will be to conduct two rounds of sampling and testing at seven sentinel sites. The program will expand to two new sentinel sites outside Oromia region. The DACA team was pleased to know that USAID/PMI program is supporting the expansion to two new sites.

Mr. Bayissa presented to the Director the amended implementation plan made by USP DQI. He asked the Director and his deputy to approve it after review so that the activities aiming at establishing a quality system in the lab will start. Dr. Smine and Dr. Wondemagegnehu discussed the benefits and challenges of getting international accreditation, but explained that they are confident that ISO 17025 certification of the DACA lab is achievable within two years (after the lab's relocation to the new facility). The Director and his deputy strongly support the accreditation of their lab to international standards. Dr. Smine explained the USP DQI approach of implementing the plan step-by-step so that the changes will not affect the work flow in the QC lab. The USP DQI team asked the Director to support the lab staff through these changes, as part of their time will be allocated to building the lab quality system. USP DQI will accompany the lab through its accreditation, pending availability of funding. The implementation plan has begun and will be monitored quarterly by USP DQI and the DACA lab director. Each step will be completed prior to the next step beginning.

The last subject discussed was the new QC lab. Dr. Smine asked to visit the new building to see where technical assistance will be needed. He urged DACA to consider hiring a professional lab designer so that the lab will comply with ISO 17025 standards. The Director stated that he invited the lab designer that USP DQI recommended, and that they will make a decision based on the recommendations that the USP DQI team makes following their visit to the new facility.

The meeting was fruitful and covered all gaps and issues affecting the drug quality monitoring program. With new DACA staff in place and with the support of the Director, his deputy, and the technical support of USP DQI, the program should be able to achieve its objectives.

Meeting with DACA sentinel sites team

Participants: USP DQI team, Director of QC lab, and three lab analysts in charge of all sentinel sites drug testing

Dr. Smine and Dr. Wondemagegnehu reviewed data sent by five sentinel sites and checked data reports, samples of antimalarials, and TLC plates. After discussion with lab analysts it was clear that the following problems have occurred:

- Medicines collected were not put in plastic containers as instructed
- Insufficient amount of tablet units were collected
- The data report sheets were not filed well
- TLC plates were not labeled as instructed
- TLC plates were sent separately from samples, making it difficult for analysts to match the samples to the TLC plates
- Some impurities were identified in some TLCs, while data reported showed no defect.
- Supervisory team did not monitor the sampling
- Sampling approach was wrongly applied in some areas. Mystery shoppers should have been used.

After discussions, the group agreed that the following should be done:

- Make sure all samples collected from sentinel sites get to QC lab
- Repeat TLC on all samples collected using TLC apparatus at the lab (large plates)
- This will allow the three staff to re-run TLC on all samples within 3-4 days
- Based on TLC data, failed and doubtful samples will be subjected to further testing using pharmacopeial methods and monographs
- Final report will be made by analysts and the supervisory team
- Work is expected to be completed in one month

After agreement on all steps to be taken, Dr. Smine discussed details about the USP DQI approach to confirmatory testing with lab analysts. The USP DQI team gave the lab director a copy of the new guidelines on medicines quality monitoring. These documents contain clear and detailed approaches for all sentinel site work, from sampling to confirmatory testing and reporting. All the forms and template needed were given to participants.

Meeting with all DACA QC lab personnel

The USP DQI team met with DACA QC lab staff to brief them and ask for their commitment to the implementation plan. Dr. Smine emphasized the importance of gaining ISO 17025 certification. It will be an important achievement for all staff that participate in the establishment of the lab quality systems and will offer new possibilities for DACA to collaborate with national and international organizations and be a leading force for quality control of medicines in Ethiopia. In the new DACA BPR, the regional DACA bureaus will develop quality control capacities; the central DACA lab will provide technical assistance to the regional labs.

Dr. Wondemagegnehu added that before getting ISO 17025 certification, the QC lab should be pre-qualified by WHO and may be become a center of excellence for drug quality in East Africa.

The Director of the lab informed the staff that upper management fully supports this initiative and that everyone in the lab should be fully committed to the project. The staff asked questions about how much time they will have to dedicate to building quality systems and how they can reach a balance between continuing to deliver their drug testing targets, and at the same time,

meet implementation plan goals. The Director of the lab promised to support all staff and keep them informed and part of the decision-making process at each step of the plan.

At the end of the meeting, the lab staff understood what it is expected of them and how important it is to work toward achieving international accreditation. The implementation plan has begun, and the QA leader is in charge of writing of the first SOPs. The tasks will be evaluated and monitored each quarter.

Visit to the new DACA building

Dr. Smine, Dr. Wondemagegnehu, and Mr. Bayissa visited the new DACA building and discussed the advances made with the building engineer. The team found that the work in the building is progressing well and is expected to be complete before the end of 2009. The team asked the engineer to give details about the Quality Control lab, which will be located on the fifth floor. He explained that they are now doing the partition by building solid walls. Part of the partition of the lab will also be made of glass-aluminum walls. The team noticed the following issues with the building of the QC lab:

- Lack of follow up by a consultant or lab specialist
- Air handling system will not comply with QC lab ISO 17025 requirements; the existing air system is only for air conditioning
- Plan will only accommodate two hoods, both on one side of the lab; at least one or two more hoods should be on the opposite side of the lab
- Entrance needs to have a double door to separate the controlled and uncontrolled lobby
- Electrical system is inadequate; very few power outlets in large rooms
- Electrical outlets must be elevated or in vertical columns
- Water system does not include piping for distilled water
- Hoods need to be connected to the air system

The engineer said that his company is under pressure to complete the building according to his plan. Soon the company will put in the tiles to cover the floor. If the electricity, water, and other work are not designed by experts, parts of the floor will have to be destroyed later. The engineer and the building consultant are not specialized in labs, so they need a specialist to instruct them about the detailed specifications.

USP DQI team recommends the following:

- Mr. Bayissa to brief the Director of DACA and his team about the issues above
- If planning and design are not done correctly, DACA will spend more money to make changes to comply with international standards and other requirements later.
- The air handling, electrical, water, and sewage systems need to be planned by a lab building expert
- The furnishing of the lab should also be done by a qualified company using flexible systems and good lasting material. The benches, hoods, and other lab furniture also need to comply with international standards.
- This work has to be done quickly to avoid waste of material and resources
- A lab consultant and the lab directors need to closely monitor the progression of work in all different labs to be established in the new building.

Meeting with Director of DACA
Participants: Mr. Yehulu Denekew, Director General, DACA; Mr. Bikila Bayissa, Director, DQCTL; Mr. Awot Gebre-izeaber, Head of QA; Dr. Eshetu Wondemagegnehu, USP DQI

The group reviewed the recommendations made by the different experts who have looked at the design of the laboratory and agreed on the following:

- It will be difficult to entertain recommendations that are made each time an expert visits the laboratory or reviews the design. Each change in design or request for delay of construction means additional costs to DACA.
- There must be a detailed examination/review of the design using appropriate experts and the necessary changes/amendments in the design or construction need to be made.
- Routine visits to the laboratory while it is under construction should be made to check for compliance. Once construction is completed, it will be difficult to make changes. There should be responsible person assigned for this.

During the walk-through of the building the team noted the following:

- The elevator and narrow stairs cannot be used for big items. There should be a heavy-duty elevator or other means for moving such things.
- There is no safety corridor leading to the emergency exit; this is particularly important in the chemistry lab.
- The number of emergency showers and eye washers in the chemistry lab is not adequate.
- The change room for staff is located on the second floor; it should be moved to the fifth floor, but if that is not possible, the sixth or fourth floor would suffice.
- The food laboratory should be located on the eighth floor.

Review of the new building design
Participants: Mr. Bikila Bayissa, Director DQCTL; Mr. Awot Gebre-igezeabher, Head of QA; Mr. Eshetu Wondemagegnehu, USP DQI

The group reviewed the design, and the following were the observations and recommendations:

Basement
There is a room labelled "CAHUU", and its purpose is not clear. The chemical store should be moved up to the ground floor. Space utilization of the gentlemen's restroom is not well designed.

Ground floor
The animal food preparation room and the food store should be moved to the basement.

Second Floor
The change rooms for lab staff should be moved to the fourth or sixth floor, and there should be a water supply for staff to wash their hands or take showers. The office for the director of the laboratory and his secretary should be moved to at least the fourth floor.

Fifth floor
Safety corridor, water supply for some of the instrument rooms, and gas supply (such as helium, nitrogen, acetylene) for some instruments needed.

Sixth Floor
There is an HVAC room and air shower, but it is not clear why they are there.

Eighth Floor
Food laboratory should be located on this floor.

Lab management should decide which equipment should be installed in which rooms so that the contractor will know the type of supplies that will be needed.

Meting with Engineers (Architect, mechanical, sanitary, etc.)
Participants: Mr. Yehulu Denekew, Director General DACA; Mr. Eshetu Wondemagegnehu, USP DQI; Mr. Megisteab Woldearegay, Deputy Director General; Mr. Bikila Bayissa, Director, DQCTL; Mr. Awot Gebre-igzeabher, Head of QA

The group walked through each floor and discussed with the engineers the issues identified during the previous meetings. The following were agreed:

- The change room needs to move to the fourth floor; the architect will work with DQCTL
- There is a need to create a safety corridor for the chemistry lab
- DQCTL will provide the contractor with the specific rooms where water, gas, and other supplies will be needed

Meeting to review lab equipment
Participants: Mr. Bikila Bayissa, Director, DQCTL; Dr. Eshetu Wondemagegnehu, USP DQI; Mr. Awot Gebre-igzeabher, Head of QA

The group identified the type and number of equipment to be installed in each laboratory room and the supplies (such as water, electricity and number of sockets, and gases) that will be needed. The group agreed that the electric supply should be 220/240v and 380v and should be three phase. Gases should be supplied centrally, where possible, particularly the butane gas.

In addition, Dr. Wondemagegnehu provided Mr. Bayissa with a copy of the revised "WHO Good Practices for Pharmaceutical Quality Control Laboratories" so that staff can work towards implementing it.

Debriefing USAID Mission
The PMI team leader, Mr. Richard Reithenger, was traveling to the field with the MOP team on Friday, May 15, so the USP DQI team could not meet with him at the end of the trip. Dr. Smine debriefed Mr. Reithenger by e-mail, summarizing the major issues discussed or resolved during USP DQI meetings with DACA and the DACA QC lab.

Conclusions
The USP DQI team met all trip objectives. The following tasks were achieved:

- USP DQI team met with MOP team to present the program's activities and future plans

- USP DQI team met with DACA executives and informed them about the pressing issues to be resolved, delay of sentinel sites activities, agreement on the implementation plan, and the technical issues about the new building.
- The implementation plan for the DACA QC lab has been amended and begun.
- The mistakes during the first phase of the drug quality monitoring program have been identified and corrective actions were put in place.
- Confirmatory testing has started
- The needs of the lab have been finalized and requests sent to USP
- DACA QC lab staff were given all guidelines to conduct confirmatory testing
- The new facility assessment was conducted and recommendations were made to DACA.

Next steps

The Director of the QC lab agreed to do the following:

- Brief the Director of DACA of the need for technical assistance to complete the partition, fitting, and furnishing the QC lab
- Submit the budget needed to complete the drug quality monitoring round, including the new changes suggested by USP DQI.
- Follow up on servicing and maintenance of the HPLCs with the South African company
- Send all samples to QC lab in Addis Ababa.
- Send USP DQI the final approved implementation plan.
- Complete all targets of the implementation plan in this quarter as planned.

After finishing TLC on all samples, the QC lab staff and USP DQI will work together to determine the plan for confirmatory testing using pharmacopeial monographs